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(54) Title: **FVII OR FVIIa VARIANTS HAVING INCREASED CLOTTING ACTIVITY**

(57) Abstract: The present invention relates to novel Factor VII or VIIa variants comprising a substitution in at least one position selected from the group consisting of L39, 142, S43, K62, L65, F71, E82 and F275, which are positions involved in tissue factor binding. Such variants exhibit increased clotting activity as compared to human wild-type Factor VIIa. The present invention also relates to use of such Factor VII or VIIa variants in therapy, in particular for the treatment of a variety of coagulation-related disorders.

WO 2004/029091 A3

## INTERNATIONAL SEARCH REPORT

International Application No

PCT/DK 03/00632

## A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C12N9/64 C07K14/745 A61K38/48 A61K38/36 A61P7/04

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C12N C07K A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, BIOSIS, WPI Data, PAJ, MEDLINE, CHEM ABS Data

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 02 38162 A (PETROVAN RAMONA J ;SCRIPPS RESEARCH INST (US); RUF WOLFRAM (US)) 16 May 2002 (2002-05-16) page 5, paragraph 2 page 7, line 13 - line 16 page 15, paragraph 2 abstract  --- -/--	1-66

☒ Further documents are listed in the continuation of box C.☒ Patent family members are listed in annex.

## \* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&amp;" document member of the same patent family

Date of the actual completion of the international search

12 March 2004

Date of mailing of the international search report

Name and mailing address of the ISA

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## INTERNATIONAL SEARCH REPORT

International Application No

PCT/DK 03/00632

## C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 01 58935 A (MAXYGEN APS) 16 August 2001 (2001-08-16)	1,2,13, 14, 16-18, 20, 24-40, 43,47, 49-59, 62-64
A	page 18, line 14 -page 30, line 34 page 50, line 34 -page 51, line 19 page 62, line 17 - line 22; claims abstract	
X	--- CHEUNG WING-FAI ET AL: "Localization of a metal-dependent epitope to the amino terminal residues 33-40 of human factor IX" THROMBOSIS RESEARCH, vol. 80, no. 5, 1995, pages 419-427, XP002273438 ISSN: 0049-3848 construct no. 3 and 4 figure 2	1-66  1,2,13, 14,16, 17,24, 51-54
X	--- DICKINSON CRAIG D ET AL: "Identification of surface residues mediating tissue factor binding and catalytic function of the serine protease factor VIIa" PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF THE UNITED STATES, vol. 93, no. 25, 1996, pages 14379-14384, XP002273439 1996 ISSN: 0027-8424 figures	1,13,24, 51-54
A	--- DICKINSON CRAIG D ET AL: "Active site modification of factor VIIa affects interactions of the protease domain with tissue factor" JOURNAL OF BIOLOGICAL CHEMISTRY, vol. 272, no. 32, 1997, pages 19875-19879, XP002273440 ISSN: 0021-9258 the whole document	1-66
A	--- SORENSEN BRIT BINOW ET AL: "Incorporation of an active site inhibitor in factor VIIa alters the affinity for tissue factor" JOURNAL OF BIOLOGICAL CHEMISTRY, vol. 272, no. 18, 1997, pages 11863-11868, XP002273441 ISSN: 0021-9258 the whole document	1-66
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## INTERNATIONAL SEARCH REPORT

International Application No

PCT/DK 03/00632

## C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	PETROVAN RAMONA J ET AL: "Residue Met156 contributes to the labile enzyme conformation of coagulation factor VIIa" JOURNAL OF BIOLOGICAL CHEMISTRY, vol. 276, no. 9, 2 March 2001 (2001-03-02), pages 6616-6620, XP002273442 ISSN: 0021-9258 the whole document ---	1-66
A	SAMPATH SRIDHARA ET AL: "Activation of a recombinant human factor VII structural analogue alters its affinity of binding to tissue factor" AMERICAN JOURNAL OF HEMATOLOGY, vol. 53, 1996, pages 66-71, XP002273443 the whole document ---	1-66
A	HIGASHI SHOUICHI ET AL: "Molecular mechanism of tissue factor-mediated acceleration of factor VIIa activity" JOURNAL OF BIOLOGICAL CHEMISTRY, vol. 271, no. 43, 1996, pages 26569-26574, XP002273444 ISSN: 0021-9258 the whole document ---	1-66
A	WO 94 27631 A (PETERSEN LARS CHRISTIAN ;NOVONORDISK AS (DK); HART CHARLES E (US);) 8 December 1994 (1994-12-08) the whole document ---	1-66
A	WO 00 66753 A (NELSESTUEN GARY L ;UNIV MINNESOTA (US)) 9 November 2000 (2000-11-09) the whole document ---	1-66
E	WO 03 093465 A (MAXYGEN HOLDINGS LTD;MAXYGEN APS ; ANDERSEN KIM VILBOUR (DK); HAAN) 13 November 2003 (2003-11-13) page 29, line 22 - line 25 ---	1-66
A	-----	1-66

# INTERNATIONAL SEARCH REPORT

International application No.  
PCT/DK 03/00632

## Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: **62-66**  
because they relate to subject matter not required to be searched by this Authority, namely:  
**see FURTHER INFORMATION sheet PCT/ISA/210**
2. ☐ Claims Nos.:  
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3. ☐ Claims Nos.:  
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

## Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this International application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

Continuation of Box I.1

Claims Nos.: 62-66

Claims 62-66 relate to methods of treatment of the human or animal body by surgery or by therapy/diagnostic methods practised on the human or animal body/Rule 39.1.(iv). Nevertheless, a search has been executed for these claims. The search has been based on the alleged effects of the compounds/ compositions.

## INTERNATIONAL SEARCH REPORT

International Application No

PCT/DK 03/00632

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